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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,533	12/17/2001	Danping Li	LA0061 NP	5618

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/023,533	LI ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-16* is/are pending in the application.

4a) Of the above claim(s) *4-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Claims 1 and 4-16 are pending in the application, but claims 1 and 11-16 are currently being prosecuted on the merits since claims 4-10 are withdrawn from consideration as being directed to a non-elected invention.

Summary of Action

2. The objection of the disclosure under 35 U.S.C. 132(a) is not maintained in light of the amendment/remarks filed August 17, 2005.

3. The rejection of claims 1 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is not maintained in light of the amendment/remarks filed August 17, 2005.

4. The rejection of claims 1 and 11-16 under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6099862) in view of Patel et al. (US 6248363 B1) and Bonhomme et al. (US 6303146) is maintained for the reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1 and 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 6099862) in view of Patel et al. (US 6248363 B1) and Bonhomme et al. (US 6303146).

Chen teaches combination of biguanide (i.e., metformin) and sulfonylurea (i.e., glipizide, glyburide (=glibenclamide), gliclazide, tolazamide, tolbutamide and etc...), namely a pharmaceutical tablet containing combination of metformin and glipizide, wherein core of said composition is prepared by mixing metformin and glipizide with povidone, sodium lauryl sulfate and magnesium stearate and then tablet is seal coated with an opadry materials (column 3, lines 6-21; Examples 1-2). As specific embodiments of the claimed invention, Examples (1-2) discloses 850mg or 500mg of metformin HCl and 5 mg of glipizide controlled release tablet,

wherein granules containing metformin and glipizide are dried "in the fluidized bed coater until the loss on drying is less than 2%" and then compressed to tablet.

Patel is being supplied as a reference to demonstrate the routine knowledge in art in preparing pharmaceutical actives such as metformin and glipizide in various pharmaceutical delivery systems including various dosage forms (e.g., tablet, capsule, quick or fast dissolving tablet, granule, etc...); coated with various coating methods (e.g., enteric coating, seal coating, protected coating or layered coating, etc...); and dosage form release system (e.g., immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release). See column 6, line 32; column 7, line 7; column 9, line 3 and 66; column 10, line 31; column 41, line 29 thru column 51, line 10.

Bonhomme discloses the combination of biguanidines (i.e., metformin) and sulfonylurea (i.e., glibenclamide (=glyburide), gliclazide, glipizide, tobutamide, tolazamide, gliquidone and chlorpropamide), namely combination of metformin and glibenclamide, wherein said combination is prepared in solid oral dosage form (i.e., tablet), and wherein said tablet is coated with hydrophilic cellulose polymer (column 1, lines 11-21; column 2, line 45 thru column 3, line 57). In addition, Bonhomme teaches the routine knowledge in maintaining 2-3% w/w moisture content prior to "tableting" (column 6, lines 37-49).

The teaching of Chen differs from the claimed invention in " being devoid of an enteric coating"; "2 to 3% by weight moisture"; and the specific dosage amounts of metformin and glipizide in said composition. However, it would have been obvious in view of Patel (US 6248363 B1) who teaches pharmaceutical delivery systems for pharmaceutical active ingredients

including metformin and glipizide, wherein said active ingredients can be prepared in various dosage forms (e.g., tablet, capsule, quick or fast dissolving tablet, granule, etc...); coated with various coating methods (e.g., enteric coating, seal coating, protected coating or layered coating, etc...); and dosage form release system (e.g., immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release), and Bonhomme who teaches the routine knowledge in art in determining 2-3% w/w moisture content prior to "tableting".

The above references in combination make clear that the combination of metformin and glipizide in single dosage formulation is old and well known in the art. The above references in combination also make clear that the preparation of pharmaceutical composition containing metformin and/or glipizide in various dosage forms (e.g., tablet, quick, fast dissolving tablet, capsule, etc...) coated with coating techniques (e.g., enteric coating, protective coating, seal coating, etc...) designed for various dosage form release systems (e.g., immediate release, controlled release, delayed release, etc...) is old and well known in the art. Furthermore, the above references in combination make clear that optimization of "less than 2%" to "2 to 3% moisture" is well within the skill of the artisan. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the instantly required "devoid of an enteric coating", Patel teaches that determination of appropriate dosage forms (e.g., tablet covered with enteric coating or with protective coating or finishing layer) having optimum therapeutic index is well considered within the skill of the artisan, ant the artisan would be motivated to determine optimum dosage forms to

maximize the effects of the drug. Therefore, the references in combination make obvious the claimed invention.

With respect to the specific dosage amounts of active ingredients in said composition, those of ordinary skill in the art readily optimize effective dosages as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information in column 5, lines 1-15.

Response to Arguments

6. Applicant's arguments filed August 17, 2005 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position similarly to the argument filed December 13, 2004 that applicant's tablets are devoid of an enteric coating and therefore are immediate release tablets. Applicant alleges that the Chen's sustained release tablets differ from the instantly claimed immediate release tablets.

Unlike applicant's assertion, there is no indication in the present claims, however that said composition must be in the form of immediate release tablets. Applicant's recitation of "being devoid of an enteric coating" does not render the claimed composition to be essentially in the form of immediate release tablet. Reading the instant claims with their "broadest reasonable

interpretation", the term "outer protective coating or finishing layer surrounding said tablet, said composition being devoid of an enteric coating" is understood as coating outer surface of tablet with any known coating techniques of pharmaceutical compositions (e.g., seal coating, film coatings, barrier coatings, compress coatings, fast disintegrating coatings, or enzyme degradable coatings) except enteric coating. Therefore, regardless of Chen's delivering of said composition in sustained release tablet or immediate release tablet, Chen's disclosure of "seal coated with an Opadry material or other suitable water-soluble material" to the tablet or core (see column 6, line 36-39; Example 2) "metes and bounds" the claimed limitation.

As discussed above, the examiner determines that "being devoid of an enteric coating" fails to confer patentability of the prior art. As evidenced by Patel, designing of diverse dosage delivery systems of pharmaceutical actives such as metformin, glipizide and glyburide (=glibenclamide) including various dosage forms (e.g., tablet, capsule, quick or fast dissolving tablet, granule, etc...); coated with various coating methods (e.g., enteric coating, seal coating, protected coating or layered coating, etc...); and dosage form release system (e.g., immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release) are well known in the art. Given the teachings of the prior art, those of ordinary skilled in the art would have been able to arrive at the claimed dosage delivery systems having optimum therapeutic index of the drugs.

In addition to Patel, the skilled artisan would have understood in view of Bonhomme that beside the specific combination of metforrmin and glibenclamide (=glyburide) combination, other combination of buguanidine (i.e., metformin) and sufonylurea (i.e., glipizide) would be similarly prepared.

As discussed above, the selection of the specific species of sulfonylurea (i.e., glipizide and glibenclamide (=glyburide)) to make combination with biguanidine such as metformin is well recognized in the art. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Applicant's argument in the response takes the position that Bonhomme does not teach or suggest the instantly claimed tablet containing metformin and glipizide containing 2-3% by weight moisture. Applicant alleges that Bonhomme refers to a loss of 2-3% w/w on drying, not 2-3% by weight moisture alleged by the applicant.

This argument is not found persuasive. Unlike the applicant's interpretation, Bonhomme's reference to "loss on drying 2-3% w/w" means "drying of composition prepared by wet granulation or other aqueous-based process substantially completely, for example to a weight loss on drying (L.O.D.) of not greater than 3%, and preferably not greater than 2%" prior to 'tableting" (see column 6, line 65 thru column 7, line 2 and column 8, lines 5-17 of US 5356896). In other words, the term "loss on drying 2-3% w/w" is routinely understood in the art as "maintaining 2-3% w/w moisture" of the granules prior to 'tableting' procedure. As discussed above, Bonhomme makes clear that the determination of "2-3% w/w by weight of moisture" is well within the skill of the artisan, especially in the art of combination of biguanide (i.e., metformin) and sulfonylurea (i.e., glibenclamide, glipizide, gliclazide, etc...).Thus, one would have been motivated to combine these references and make the modification because they are

drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. No Claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (703) 872-9306.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Brian Kwon
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AU 1614

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